PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 2203445-WO0	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2007/075555	International filing date *(day/month/year)* 09 August 2007 (09.08.2007)	Priority date *(day/month/year)* 09 August 2006 (09.08.2006)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CYPRESS BIOSCIENCE, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 10 February 2009 (10.02.2009)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Masashi Honda e-mail: pt08.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
S. PETER LUDWIG
DARBY & DARBY P.C.
P.O. BOX 770
CHURCH STREET STATION
NEW YORK, NY 10008-0770

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	12 SEP 2008
Applicant's or agent's file reference 2203445-WO0	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US07/75555	09 August 2007 (09.08.2007)	09 August 2006 (09.08.2006)

International Patent Classification (IPC) or both national classification and IPC

IPC: **A61K 31/165**(2006.01);**A61P 25/28**(2006.01) A61K 31/165(2006.01);A61P 25/28(2006.01)
USPC: 514/620

Applicant

CYPRESS BIOSCIENCE, INC

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	27 August 2008 (27.08.2008)	Sreeni Padmanabhan Telephone No. (571) 272-1600

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
   - ☒ the international application in the language in which it was filed
   - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material
      - ☐ a sequence listing
      - ☐ table(s) related to the sequence listing

   b. format of material
      - ☐ on paper
      - ☐ in electronic form

   c. time of filing/furnishing
      - ☐ contained in the international application as filed.
      - ☐ filed together with the international application in electronic form.
      - ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-12	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-12	NO
Industrial applicability (IA)	Claims 1-12	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-12 lack an inventive step under PCT Article 33(3) as being obvious over Rao et al. (US 2004/0106681 A1).

The instant claims are directed to a method of treating a fatigue symptom associated with fibromyalgia syndrome (FMS) comprising administering milnacipran in greater than about 125 mg per day to a patient in need thereof, or administering milnacipran adjunctively with a second active compound such as valium.

Kranzler et al. teach a method of treating fibromylagia syndrome (FMS) comprising administering a therapeutically effective amount of dual serotonin norepinephrine reuptake inhibitor such as milnacipran (see abstract; column 2, lines 40-61). Kranzler et al. teach daily dosage ranges for treatment of FMS with milnacipran of 25 to 400 mg/day, or more typically 100-250 mg/day. The dosage may be administered once per day, or multiple times per day (see column 12, lines 16-29). Kranzler et al. further teach milnacipran can be adjunctively administered with other active compounds such as valium (see columns 7-8, lines 18).

Kranzler et al. do not explicitly teach treating a fatigue symptom associated with fibromyalgia, or maintaining a daily dosage of milnacipran for at least 3 months, or at least 6 months as claimed in the instant claims 5-6.

However, it would have been obvious to one of ordinary skill in the art at the time of the invention that in treating fibromyalgia with the dosage guidelines as taught by Kranzler et al., a fatigue symptom associated with the fibromyalgia would also be treated. One of ordinary skill in the art would have been motivated to do so in order to treat fibromyalgia in general. One of ordinary skill in the art would have had a reasonable expectation of success in also treating a fatigue symptom because Kranzler et al. use overlapping dosage ranges of milnacipran as claimed for the treatment of fibromyalgia. Thus, the patient populations would significantly overlap. Furthermore, the optimization of the duration of the dosing regime of milnacipran is considered to be within the purview of the ordinary artisan.

Claims 1-6 and 9-11 lack an inventive step under PCT Article 33(3) as being obvious over Rao et al. (US 2004/0106681 A1).

Rao et al. teach treating neurological disorders such as fibromyalgia by administering high daily dosages of antidepressant, such as milnacipran (see abstract; page 1, section [0005]; page 2, section [0028]). Higher dosages of the drug to improve efficacy without adverse side effects are achieve by escalating the dosages over time and/or dividing the daily into divided doses (see abstract). Rao et al. further teach that milnacipran is preferably administered between 100 mg/day to 400 mg/day, and more preferably administered in 200 mg/day to 300 mg/day, wherein the daily dosage is divided into two daily doses (see page 8, sections [0133]-[0137]). In specific examples, Rao et al. teach treating fibromyalgia with

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Supplemental Box
In case **the space in any of the preceding boxes is not sufficient**.

escalated divided dosages of milnacipran, wherein the end daily dosage is 200 mg/day and maintained for 8 weeks after reaching said dosage. Rao et al. teach that higher dosages of (i.e. 200 mg/day) and divided dosages were more effective in relieving pain than lower once daily dosing (see Examples 1-2, pages 9-11, sections [0162] to [0187]).

Rao et al. do not explicitly teach treating a fatigue symptom associated with fibromyalgia, or maintaining a daily dosage of milnacipran for at least 3 months, or at least 6 months as claimed in the instant claims 5-6.

However, it would have been obvious to one of ordinary skill in the art at the time of the invention that in treating fibromyalgia with using higher divided daily dosages as taught by Rao at al., a fatigue symptom associated with the fibromyalgia would also be treated. One of ordinary skill in the art would have been motivated to do so in order to treat fibromyalgia in general. One of ordinary skill in the art would have had a reasonable expectation of success because Rao et al. teach using the same higher multiple dosing regimes (i.e. 200 mg/day) of milnacipran as claimed for the treatment of pain associated with fibromyalgia. Thus, the patient populations significantly overlap. The optimization of the duration of the dosing regime of milnacipran is considered to be within the purview of the ordinary artisan.

Claims 7-8 lack an inventive step under PCT Article 33(3) as being obvious over Rao et al. (US 2004/0106681 A1) in view of Kranzler et al. (US 6,602,911 B2).

Rao et al. is described *supra*, as applied to claims 1-5 and 8-11.

Rao et al. do not teach adjunctively administering a second compound for the treatment of a fatigue symptom associated with FMS, wherein the second compound is for example valium.

Kranzler et al. is described *supra*, as applied to claims 1-11. As previously stated, Kranzler et al. teach administering milnacipran adjunctively with a second active compound such as valium for the treatment of FMS.

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat a fatigue symptom associated with FMS with milnacipran as obvious over Rao et al., and with an adjunctively administered compound such as valium as taught by Kranzler et al. One of ordinary skill in the art would have been motivated to so with a reasonable expectation of success because both Rao et al. and Kranzler et al. teach similar dosages of milnacipran for treating FMS.